

## Case Report

# HITT or Miss

Michael Kinney<sup>1</sup>, Thomas Peukert<sup>1</sup>, Stephen McKinstry<sup>1</sup>, Gary Benson<sup>2</sup>, Paul McMonagle<sup>1</sup>

Accepted 20 June 2013

## INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is not infrequently seen by neurologists, who must undertake an extensive search for an underlying cause. Infrequently patients may undergo a second CVST event, and here we present a case of heparin induced thrombocytopenia and thrombosis as the cause of the recurrence of a CVST.

## CASE REPORT

A 40-year old right handed female developed an acute left temporal headache, nausea, and neck stiffness which worsened over 2 days preceding admission, and then evolved to become a generalised headache. For the preceding 4 months she had intermittent left sided headache. She had a history of type II diabetes, controlled on metformin, and had severe iron deficiency anaemia secondary to menorrhagia for 3 years.

On initial examination she was photophobic with expressive dysphasia, and had left to right disorientation, with no frank papilloedema. Cranial nerve and peripheral nervous system examination were otherwise normal. CT brain on day 2 of admission (figure 1a) identified a filling defect in the left transverse and the sigmoid sinuses consistent with acute thrombosis, causing secondary left temporal-parietal haemorrhage.

She was commenced on an intravenous unfractionated heparin infusion, after being given an intravenous bolus of 5000 units. The rate of infusion was initially 1.7 ml/hr based on her weight which was 116kg. The target range for her activated partial thromboplastin time (APTT) was 44-84 seconds, and was achieved within hours. Her headache resolved by day 10. A repeat CT scan on day 11 of admission (figure 1b) showed improvement with reduction in the size of the haematoma, and venography demonstrated a degree of recanalization with some flow identified within the left transverse sinus however thrombus was still present.

Due to the severe symptomatic anaemia, despite being on oral iron supplementation, she was transfused 5 units of packed red cells during her admission. It was decided that she should undergo definitive treatment for her longstanding menorrhagia and on day 22, she had an endometrial ablation and sterilisation. Her heparin infusion was stopped for only a few hours during this procedure. Of note her APTT

Neuroimaging over the course of the admission.



*Fig 1.* CT venogram (Figure 1a) on admission shows no enhancement of the left sigmoid sinus due to thrombosis. Thrombus also extended into the left jugular bulb and transverse sinus. CT venogram (Figure 1b) following treatment shows recanalisation of left sigmoid sinus with a small filling defect consistent with residual thrombus. MR venogram (Figure 1c) after recurrence of symptoms shows absent flow in left transverse and sigmoid sinuses and jugular vein, indicating recurrent thrombosis.

pre procedure was 62 seconds, and post procedure was 25 seconds. The infusion was restarted and the rate increased to bring her back to target range, however this initially over compensated, and the initial APTT was 107 seconds after the dose adjustment.

However a global headache returned by day 23. Of note, two days after her headache returned her platelet count fell below 50% of her peak platelet count. (Figure 2.  $398 \times 10^9/L$  on day 19, to  $186 \times 10^9/L$  on day 25) The platelet count continued to fall and by day 30 was  $52 \times 10^9/L$ . At this point subcutaneous therapeutic dose enoxaparin (110mg twice daily) which had been started with a view to warfarinising the patient, was switched back to unfractionated heparin. With the on-going headache, magnetic resonance venography (figure 1c) was carried out showing no detectable flow in the left sigmoid or the internal jugular bulb.

HITT was considered given the low and falling platelet count, and the neuroimaging confirming the reaccumulation of the thrombosis. A HITT enzyme-linked immunosorbent assay (ELISA) assay was carried out and was strongly positive, with an optical density of 1.67. This is associated with a risk of thrombosis in greater than 50% of cases. Her Intravenous

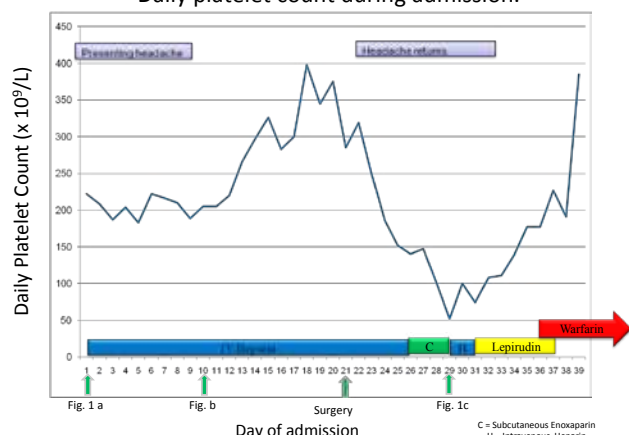
<sup>1</sup>Department of Neurology and <sup>2</sup>Radiology, The Royal Hospitals, 274 Grosvenor Road, Belfast. BT12 6BA. <sup>2</sup>Department of Haematology, Belfast City Hospital, 51 Lisburn Road, Belfast, BT9 7AB

mickinney@gmail.com

Correspondence to: Dr Michael Kinney

heparin was stopped, and she was commenced on a direct thrombin inhibitor, lepirudin. This was made up of 100mg in 50mls sodium chloride. It was commenced as a continuous intravenous infusion, and ran at 0.15mg/Kg body weight/hr. In this case 8.3ml/hr, aiming for a target of 45-70 seconds. Her APTT was within range within 10 hours. Once her platelet count was above  $100 \times 10^9/L$ , she was cautiously warfarinized, with daily 5mg dose of warfarin. The headache settled the day after starting lepirudin, and her platelet count normalised, and she was established on warfarin, and remained well at 1 year review.

Daily platelet count during admission.



## DISCUSSION

Heparin-induced thrombocytopenia is a potentially fatal condition that occurs mainly as a result of exposure to unfractionated heparin<sup>1</sup>. It can also occur after exposure to low molecular weight heparin, and fondaparinux. It is caused by antibodies against both platelet factor 4 (PF4) and heparin complexes, and can occur after exposure to heparin in any quantity and via any route. A clinical scoring system is used in conjunction with assay tests to confirm the diagnosis<sup>1</sup>.

Thrombosis typically occurs in 20-50% of HIT positive patients<sup>1</sup>. 12 reports of CVST with HIT after the use of unfractionated heparin have been reported in the literature and 1 case after the use of low molecular weight heparin (LMWH)<sup>1</sup>. HIT with CVST typically has a high mortality, estimated to be approximately 40% in this small case series<sup>2</sup>. This is related to delayed diagnosis, and delayed appropriate management. Of the previously published cases there were marked differences in the investigations and subsequent management of patients (table 1)<sup>2,3</sup>.

Anticoagulation, with a non-heparin based medication, is the treatment of choice for this thrombotic condition<sup>1</sup>.

This case is interesting from the perspective that an initial thrombus suspected to have been caused by chronic iron deficiency anaemia<sup>4,5</sup> recollected in the context of developing HIT secondary to IV heparin treatment. This case is also one with a favourable outcome, despite the delay in diagnosis, by potentially 1 week. Typically HIT develops in cases within 5-10 days, but up to 15 days of exposure to heparin, if the patient has never been exposed before, or the exposure was

TABLE 1:

Summary of the 12 cases reported in the literature.

Parameter	Patient details
Mean age	43 y old (8F: 3M) one not reported
% in context of operative procedure	45%
Treatment employed	5 treatments were not reported. 3 warfarin (2/3 survived) 1 LMWH (patient died) 1 Lepirudin (outcome NR) 1 Argatroban and endovascular mechanical thrombolysis. (patient died) 1 Fondaparinux (survived)
Survival	50% (5/10 reported outcomes)

greater than 100 days prior. If an exposure to heparin occurs in someone who has recently been sensitized to heparin in the previous 100 days, and they have already developed antibodies against PF4 and heparin, then the fall in platelet count can occur within hours<sup>1</sup>. In this case her platelet count fell by >50% of peak by day 25 of treatment with IV heparin. It is possible that this case represents a rare variant of HIT, which presents on the cessation of heparin. So called rapid-onset HIT may in this case have been triggered by the cessation of heparin during her gynaecological procedure on day 23. The importance of frequently reviewing the platelet count of patients on heparin and also LMWH cannot be overstated. To this end it is recommended that platelets should be monitored on alternate days between days 5-15 of treatment to ensure the diagnosis of HIT is picked up.

## CONCLUSION

This case draws attention to the importance of considering the extensive range of possible causes of CVST, including HIT. It also serves to highlight the importance of platelet count monitoring in patients on unfractionated heparin regimes, and seeking expert advice when significant changes occur, especially in the context of a new or recurring thrombosis.

The authors have no conflict of interest.

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